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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/510,064	02/13/2006	Kamalakar Talasila	GEN 3.3-015	4267

45776 7590 10/20/2010

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ART UNIT	PAPER NUMBER
1625	

NOTIFICATION DATE	DELIVERY MODE
10/20/2010	ELECTRONIC

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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/510,064
Filing Date: February 13, 2006
Appellant(s): TALASILA ET AL.

Kenneth M. Zeidner
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 19, 2010 appealing from the Office action mailed Feb. 19, 2010.

(1) Real Party in Interest

The examiner has no comment on the statement, or lack of statement, identifying by name the real party in interest in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of status of claims that were finally rejected in the Office action mailed February 19, 2010 and are the *subject* of this appeal should be the examined subject matter that is claims 18-36 in light of the restriction. The Office action dated February 19, 2010 clearly stated the *subject* matter and claims being examined were:

> "The elected claim 37 wherein the antihistamine is fexofenadine hydrochloride form X with cellulose, mannitol, starch and croscarmellose, and the decongestant is a salt of pseudoephedrine and polyvinylacetate and povidone, thus, i.e. group I and claims 18-36 (correction of typographic error 18-35) reading on the elected subject matter are pending." (See p.2)
>
> Claims 1-17 have been canceled. The remaining subject matter wherein antihistamine is selected from Fexofenadine (excluding hydrochloride in form X), Loratadine, Terfenadine, Cetrizine or a pharmaceutically acceptable salts thereof, or a decongestant selected fromPseudoephedrine, phenylephrine, phenylpropanolamine stayed withdrawn from consideration per 37 CFR 1.142(b). (see p.2)

The restriction has been made final in the Office action dated April 23, 2009. Propriety of restrictable subject matter can be petitioned but is not appealable. MPEP 818.03(c) stated that: *37 CFR 1.144. Petition from requirement for restriction.*

> **>After a final requirement for restriction, the applicant, in addition to making any reply due on the remainder of the action, may petition the Director to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested (see § 1.181).<

Please note that no petition was filed in the record.

(4) Status of Amendments After Final

The examiner has no comment on the appellant's statement of the status of amendments after final rejection contained in the brief.

(5) Summary of Claimed Subject Matter

The statement of the claimed subject matter under examination is erroneous. The claimed subject matter being examined is claim 37 as appeared on replacement p.7-8:

Independent claim 37 is directed to a pharmaceutical composition comprising:

a) a tablet layer comprising crystalline form X of fexofenadine hydrochloride, about 20 to about 45 percent by weight cellulose, about 10 to about 30 percent by weight mannitol, about 5 to about 25 percent by weight starch, and about 4 to about 15 percent by weight of a disintegrant *(See Example 1, Step A: Formulation (A), in the table on page 10 after line 13);* and

b) a tablet layer comprising a salt of pseudoephedrine and about 40 to about 80 percent by weight of a mixture comprising about 80 percent polyvinyl acetate and about 19 percent povidone *(See Example 1, Step B: Formulation (B) , in the table on page 11 after line 5).*

No claim depends from this independent claim.

(6) Grounds of Rejection to be Reviewed on Appeal

The examiner has no comment on the appellant's statement of the grounds of rejection to be reviewed on appeal. Every ground of rejection set forth in the Office action from which the appeal is taken (as modified by any advisory actions) is being maintained by the examiner except

for the grounds of rejection (if any) listed under the subheading "WITHDRAWN REJECTIONS."

WITHDRAWN REJECTIONS

The following grounds of rejection are not presented for review on appeal because they have been withdrawn by the examiner. The rejections under 35 USC 112 first paragraph and 35 USC 103(a) for independent claim 37 are withdrawn.

(7) Claims Appendix

The examiner has no comment on the copy of the appealed claims contained in the Appendix to the appellant's brief

(8) Evidence Relied Upon

6,039,974	MacLaren et al.	3-2000
6,210,712	Edgren et al.	4-2001
6,627,646	Bakale et al.	9-2003
2005/0256163	Kor et al.	11-2005

Muzaffar et al. "Polymorphism and drug availability" J. Phar. 1(1) 59-66 (1979)

Jain et al. "Polymorphisom in pharmacey" Indian Drugs 23(g)315-329 (1986)

Doelker et al. "Crystalline modification…." CA 138:209993 (2002)

Doelker et al. "Physicochemical behavior or active…." CA 132:325872 (2000)

Otsuka et al. "effect of polymorphic…." Chem. Pharm. Bull, 47(6) 852-856 (1999)

CMU Pharmaceutical polymorphism, internet p.1-3 (2002) (print out 4/3/2008)

Singhal et al. "Drug polymorphism……" Advanced drug delivery reviews 56. p.335-347 (2004)

Pharmacopedia "Tablet:formulation……" (2009) p.1-7, internet

Buhler "POlyvinylpyrrolidone……" p.179-183 (2009 from internet)

Ahjel et al. :Directely compressible…." Farmacia (2008) v. LVI(6) 591-599.

US Pharmacopia #23, national formulary #18, (1995) p.1843.

(9) Grounds of Rejection

The following grounds of rejection are applicable to the appealed claims:

(A) In the record claims 37 and 18-36 limited to the elected subject matter are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contain subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. This rejection is withdrawn with respect to claim 37 in this examiner's answer.

The claims are drawn to a composition containing fexofenadine hydrochloride Form X in a bilayer composition with pseudoephedrine. The maintenance of the "Form X' in a composition depends unpredictably on its process steps. Any step that dissolves the active compound in its crystalline form would not result in a composition that contains such a *form.* It is noted that on page 10, lines 14-17, it was described:

> *"Sift Fexofenadine hydrochloride (Form X/A), mannitol, powdered cellulose, crosscarmellose sodium and colloidial silicon dioxide through mesh #20 screen. Sift corn starch iron oxide red through mesh #80 screen. Mix the sifted material in rapid mixer granulator (RMG) for about 25 minutes. Mix the obtained dry mix from RMG with isopropyl alcohol to obtain desired wet mass."*

The mixing with solvent isopropanol has been recognized in the prior art to dissolve fexofenadine hydrochloride (See US 2005/0256163, p.8, example 7). Dissolution of the

crystalline form will result in a composition containing amorphous fexofenadine hydrochloride not the crystalline form X.

To the extent that the dry powder can be directly pressed into tablet, it is noted in preponderance of art that absent of factual evidence, such compression would result in transformation or disappearing of the crystalline form and a Wands analysis is made below:

Claims 37 and claims 18-36 limited to the elected subject matter are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention, or was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

It is well known in the art, at a given pressure and temperature only one thermo-dynamically stable crystalline form will exist for a given compound (US pharmacopeia, copy was not in file but now attached). It is further well recognized in the art that when a crystalline form for a drug is prepared into a solid formulation, *unless specific and particular* conditions can be described, the "form" is expected to change to the most thermodynamically stable one.

See :

Muzaffar et al. p.60 "At any one temperature and pressure only one crystal form of a drug is stable and any other polymorph existing under these conditions will convert to the stable form …." And p.63-65 (a)-(h) pharmaceutical preparing processes affect polymorphism;

Jain et al. p.322-326, manufacturing processes that affect polymorphs ;

Doelker et al. abstract, "One may also observe changes in technology or pharmaceutical properties that are due to polymorphic environmental conditions undergone by the product or the dosage form"

Doelker et al. abstract "…a given drug, although chem. well defined, may exhibits quite different behavior. Process conditions (*grinding, tableting, granulations, drying)* may also affect secondary properties of the drug, such as compactibility, wetttability, soly, dissoln, rate, bioavailability and even pharmacol. activity."

Otsuke et al. p.852 « …in formulation studies and the method preparing CBZ has been shown to affect the drug's pharmaceutical properties through the polymorphic *phase transformation* of the bulk CBZ powder during the manufacturing process"

Singhal et al. "..It should be pointed out that a major portion of any formulation effort is the choice of exipients and processes which minimize the chemical instability of the drug…." P.338, left col.

CMU phar. Polymorph. "there are a number of examples in which polymorphic molecules change crystal structure under processing conditions while in contact with liquids or solid material. In these environments, it is difficult to apply standard techniques to identify the predict the transformation…." See p.1-2 paragraph bridging.

US 6,627,646, col. 1-2, especially, "..from thermodynamic considerations only one polymorph will be stable;.....however, thermodynamic stability is not sufficient to ensure that the stable polymorph will always be produced…….most transformations occur in suspension and are solvent mediated…..other transformations are irreversible over a broad range of temperature:

The specification provided enablement as to how the crystalline form X can be prepare into a composition which can maintain the particular crystalline structure without the conventional recognized conversion to its thermodynamic form. Per ponderous of evidence in the prior art indicated that for a given polymorph, *absent of factual evidence* the compression process as disclosed does not *automatically* keeps the original form in the pharmaceutical composition. Absent of this composition, the bilayer composition with "form X" lacks enablement.

(B) Claims 37 and 18-36 limited to the elected subject matter are rejected under 35 U.S.C. 103(a) as being unpatentable over MacLaren et al. US 6,039,974 (recited on 1449) in view of Pharmapedia or Ahjel further in view of Edgren et al. US 6,210,712 and Buhler. This rejection is withdrawn for claim 37.

Determination of the scope and content of the prior art (MPEP §2141.01)

MacLaren et al. '974 disclosed bilayer composition containing a layer of antihistamine fexofenadine in immediate release formulation and a layer of pseudoephedrine in sustain release formulation.

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

The difference between the instant claims and the prior art is that in the immediate release formulation, the elected active ingredient (in its dissolved form as explained supra),

cellulose, starch and croscamellose sodium have been found (see col. 12 table 1) the other elected ingredient *mannitol* was not employed. Generically, the immediate release layer was describe to optionally contain a diluent such as lactose (see col. 11 lines 25-35). Pharmapedia or Ahjel et al. taught that mannitol and lactose are optional choices of diluent. The difference between the instant elected sustained release layer and the prior art is that the instant sustained release layer contains pyrrolidone and vinyl acetate. Pyrrolidone and vinyl acetate sustained release formulation has been conventionally known (see Edgren et al. '712 example 4, pseudoephedrine and pyrrolidone col. 13-14 and generically, the binder is pyrrolidine or optionally a mixture of other vinyl monomers including vinyl acetate see col. 6 lines 14-33).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art in possession of the above references is in possession of the optional choices of diluent or the alternative sustained release pseudoephedrine formulation. The picking and choose of an *alternative* diluent to be incorporated into a bilayer system of the prior art as a sustained release layer of a conventionally prepared composition is prima facie obvious. Because, it is well taught in the prior art that the fexofenadine is prepared in an immediate release formulation and the other layer is a sustain release formulation of pseudoephedrine, in the instant claims, the modification is povidone and vinyl acetate which substitution is motivated by the conventional marketed material for sustained release (see Buhler).

In response to Appellants' argument that "any fexofenadine hydrochloride not having form X crystal structure would be outside the scope of claim 37 and Appellants are in possession of such a composition" (see brief p.14-15); a survey of the specification provided that the formula A which is fexofenadine hydrochloride form X in admix with 20-24% cellulose, 10-30% mannitol, 5-25% starch, 4-15% disintegrant has a demarcated disintegration profile from the non-form X allegra (see p. 11 comparison table), thus, are in possession of "fexofenadien hydrochloride form X" bilayer tablet. Therefore, the rejection of claim 37 under 35 USC 112 and 103(a) are dropped.

Claim 37 is allowable.

(10) Response to Argument

(A) Appellants argued that:

The specification described that the dry mixture of "form X" from the granulator is mixed with isopropanol to obtain a "desired wet mass", therefore, even if conversion occurs, as

long as some "Form X" remains, the non-form X composition would be outside the scope of the claims.

The examiner's position is:

A survey of the specification was made and the possession of form X composition showing different dissolution profile from the non-form X composition supported appellants' argument to the extent of claim 37.

The office has provided preponderance of evidence indicating the unpredictable nature of such formulation art (see Muzaffar, Jain, Doelker, Otsuke, Singhal, CMU phar or US 6,627,646, supra). While specific carrier can keep measurable amount of a particular crystalline form, it is well recognized facts that ordinary pharmaceutical carrier or unlimited wet processing would not be operable.

(B) Appellants agued that:

The MacLaren reference would not provide the specific fexofenadine hydrochloride form X, therefore, no obviouness over the non-form X should be made in an unpredictable field of endeavor.

The examiner's position is:

In view of the preponderance of evidence that unless supported by factual evidence, ordinary pharmaceutical carrier or wet processing such as MacLaren's without mannitol would not maintain any crystalline form. The factual support from p.11 of the specification, showing that the carrier composition of 20-24% cellulose, 10-30% mannitol, 5-25% starch, 4-15% disintegrant would maintain the crystalline form X and its different dissolution property from the non-crystalline form X, is unexpectancy, thus, claim 37 is neither anticipated nor rendered obvious in view of table of p.11.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that claim 37 is allowable upon cancellation of claims 18-36 per MPEP 818.03(d) which says:

818.03(d) [R-3] Traverse of **>Restriction Requirement With< Linking Claims
** Election >of a single invention in reply to a restriction requirement,< combined with a traverse of >only< the nonallowance of the linking claims*>,< is an agreement with the

position taken by the Office that restriction is proper if the linking* claim is not allowable and improper if **>it is< allowable. If the Office allows such a claim, it is bound to withdraw the requirement and to act on all linked inventions >which depend from or otherwise require all the limitations of the allowable linking claim<. But once all linking claims are canceled 37 CFR 1.144 would not apply, since the record would be one of agreement as to the propriety of restriction.
Where, however, there is a traverse on the ground that there is some relationship (other than and in addition to the linking* claim) that also prevents restriction, the merits of the requirement are contested and not admitted. ** If restriction is made final in spite of such traverse, the right to petition is preserved even though all linking claims are canceled.
>When a final restriction requirement is contingent on the nonallowability of the linking claims, applicant may petition from the requirement under 37 CFR 1.144 without waiting for a final action on the merits of the linking claims or applicant may defer his or her petition until the linking claims have been finally rejected, but not later than appeal. See 37 CFR 1.144 and MPEP § 818.03(c).<

Respectfully submitted,

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